PI 1164418

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

May 06, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *60/455,932*
FILING DATE: *March 19, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/07793*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

M. Sias

M. SIAS
Certifying Officer

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

03-20-03 60455932 - U.S. PTO

SUBSTITUTE for Provisional Application for Patent Cover Sheet PTO/SB/16 (10-01)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

03/19/03 JJ133 U.S. PTO

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under 37 CFR 1.53 (c).

60/455932 U.S. PTO 03/19/03 c997

DOCKET NUMBER	21178PV

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Yi	Xiao	Fanwood, New Jersey
Joseph D.	Armstrong, III	Westfield, New Jersey
Shane W.	Krska	New Providence, New Jersey
Eugenia	Njolito	Princeton, New Jersey
Nelo R.	Rivera	New Milford, New Jersey

☐ Additional inventors are being named on the separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

PROCESS TO CHIRAL BETA-AMINO ACID DERIVATIVES BY ASYMMETRIC HYDROGENATION

CORRESPONDENCE ADDRESS

Direct all Correspondence to:

Merck & Co., Inc.
Patent Department - RY60-30
P.O. Box 2000
Rahway

☒ Customer Number 000210

STATE	New Jersey	ZIP CODE	07065	COUNTRY	U.S.A.

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification — *Number of Pages* 24
☐ Drawing(s) — *Number of Sheets*
☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number
☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☐ A check or money order is enclosed to cover the filing fees

☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 13-2755

FILING FEE AMOUNT ($) $160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE Philippe L Durette

TYPED or PRINTED NAME Philippe L. Durette

TELEPHONE 732-594-4568

Date 03/19/2003

REGISTRATION NO. (if appropriate) 35,125

EXPRESS MAIL CERTIFICATE

DATE OF DEPOSIT March 19, 2003

EXPRESS MAIL NO. EL 920632995 US

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL "POST OFFICE TO ADDRESSEE" ON THE ABOVE DATE IN AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231.

MAILED BY Kathy Kulikowski DATE 3-19-03

In Duplicate

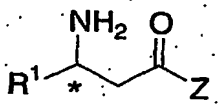
TITLE OF THE INVENTION
PROCESS TO CHIRAL BETA-AMINO ACID DERIVATIVES BY ASYMMETRIC HYDROGENATION

FIELD OF THE INVENTION

The present invention relates to a process for the efficient preparation of enantiomerically enriched beta-amino acid derivatives which are useful in the asymmetric synthesis of biologically active molecules. The process comprises an enantioselective hydrogenation of a prochiral beta-amino acrylic acid derivative precursor in the presence of a transition metal catalyst complexed with a chiral ferrocenyl diphosphine ligand.

BACKGROUND OF THE INVENTION

The present invention provides an efficient process for the preparation of an enantiomerically enriched beta-amino acid derivative of structural formula I:

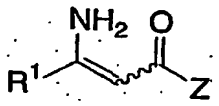


(I)

having the (*R*)- or (*S*)-configuration at the stereogenic center marked with an *;
wherein
Z is OR^2, SR^2, or NR^2R^3;
R^1 is C_{1-8} alkyl, aryl, heteroaryl, aryl-C_{1-2} alkyl, or heteroaryl-C_{1-2} alkyl;
R^2 and R^3 are each independently hydrogen, C_{1-8} alkyl, aryl, or aryl-C_{1-2} alkyl; or
R^2 and R^3 together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclic ring system optionally containing an additional heteroatom selected from O, S, and NC_{1-4} alkyl, said heterocyclic ring system being optionally fused with a 5- to 6-membered saturated or aromatic carbocyclic ring system or a 5- to 6-membered saturated or aromatic heterocyclic ring system containing one to two heteroatoms selected from O, S, and NC_{1-4} alkyl, said fused ring system being unsubstituted or substituted with one to two substituents independently selected from hydroxy, amino, fluoro, C_{1-4} alkyl, C_{1-4} alkoxy, and trifluoromethyl.

The process of the present invention relates to a method for the preparation of chiral beta-amino acid derivatives of structural formula I in an efficient

enantioselective fashion *via* transition metal-catalyzed asymmetric hydrogenation of a prochiral enamine of structural formula II:



(II)

wherein the enamine amino group is unprotected, in the presence of a chiral ferrocenyl diphosphine ligand.

A method for asymmetrically reducing enamine carbon-carbon double bonds (C=C-N) using chiral ferrocenyl diphosphines as ligands complexed to a rhodium or iridium catalyst has been described in the patent literature (See U.S. Patent No. 5,563,309 issued Oct. 8, 1996 to Ciba-Geigy Corp. and the related family of patents and patent applications). A related approach to *N*-acylated beta amino acids using a rhodium Me-DuPHOS catalyst complex has also published (U.S. 2002/0128509 published on Sept. 12, 2002 assigned to Degussa AG). The following publications also describe the asymmetric hydrogenation of *N*-acylated beta-amino acrylic acids with rhodium catalysts complexed to a chiral phosphine ligand: (1) T. Hayashi, et al., Bull. Chem. Soc. Japan, 53: 1136-1151 (1980); (2) G. Zhu et al., J. Org. Chem., 64: 6907-6910 (1999); and (3) W. D. Lubell, et al., Tetrahedron: Asymmetry, 2: 543-554 (1991). In these publications all the examples provided have the enamine amino group in the beta-amino acrylic acid derivative precursor protected as an acetamide derivative. The requirement for amine protection introduces two additional chemical steps into the sequence, namely protection and deprotection, and the synthesis of the protected substrate may also be difficult. The process of the present invention circumvents the need for protecting the amino group in the substrate for the asymmetric hydrogenation reaction and proceeds with excellent reactivity and enantioselectivity.

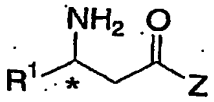
SUMMARY OF THE INVENTION

The present invention is concerned with a process for the preparation of enantiomerically enriched beta-amino acid derivatives of structural formula I. The process utilizes an asymmetric hydrogenation of a prochiral beta-amino acrylic acid derivative, wherein the enamine amino group is unprotected, in the presence of a transition metal catalyst complexed with a chiral ferrocenyl diphosphine ligand. The

process of the present invention is applicable to the preparation of beta-amino acid derivatives on a pilot plant or industrial scale. The beta-amino acids are useful to prepare a wide variety of biologically active molecules.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an efficient process for the preparation of an enantiomerically enriched beta-amino acid derivative of structural formula I:



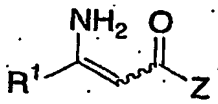
(I)

having the (*R*)- or (*S*)- configuration at the stereogenic center marked with an *; in an enantiomeric excess of at least 70% over the opposite enantiomer, wherein Z is OR^2, SR^2, or NR^2R^3;

R^1 is C_{1-8} alkyl, aryl, heteroaryl, aryl-C_{1-2} alkyl, or heteroaryl-C_{1-2} alkyl;

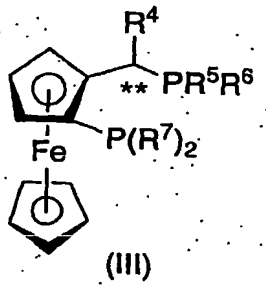
R^2 and R^3 are each independently hydrogen, C_{1-8} alkyl, aryl, or aryl-C_{1-2} alkyl; or R^2 and R^3 together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclic ring system optionally containing an additional heteroatom selected from O, S, and NC_{1-4} alkyl, said heterocyclic ring system being optionally fused with a 5- to 6-membered saturated or aromatic carbocyclic ring system or a 5- to 6-membered saturated or aromatic heterocyclic ring system containing one to two heteroatoms selected from O, S, and NC_{1-4} alkyl, said fused ring system being unsubstituted or substituted with one to two substituents selected from hydroxy, amino, fluorine, C_{1-4} alkyl, C_{1-4} alkoxy, and trifluoromethyl.

The process of the present invention comprises the step of hydrogenating a prochiral enamine of structural formula II:



(II)

in a suitable organic solvent in the presence of a transition metal catalyst complexed to a chiral ferrocenyl diphosphine ligand of structural formula III:

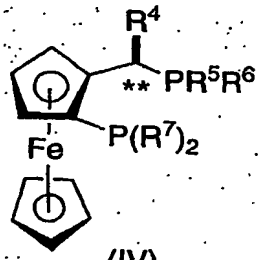


(III)

wherein R^4 is C_{1-4} alkyl or aryl;
R^5 and R^6 are each independently C_{1-6} alkyl, C_{5-12} cycloalkyl, or aryl; and
R^7 is C_{1-4} alkyl or aryl.

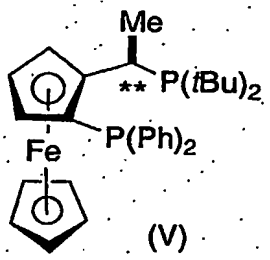
The ligands of structural formula III are known in the art as Josiphos ligands and are commercially available from Solvias AG, Basel, Switzerland.

In one embodiment of the ligands of formula III useful in the process of the present invention, the carbon stereogenic center marked with an ** has the (*R*)-configuration as depicted in formula IV:



(IV)

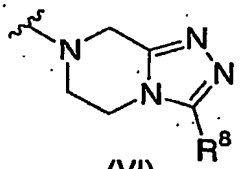
In another embodiment of the ligands of formula III useful in the process of the present invention, R^4 is C_{1-2} alkyl, R^5 and R^6 are C_{1-4} alkyl, and R^7 is phenyl. In a class of this embodiment, R^4 is methyl, R^5 and R^6 are *t*-butyl, and R^7 is phenyl. The latter ligand is known in the art as *t*-butyl Josiphos. Commercially available forms of the *t*-butyl Josiphos ligand are the *S,R* and *R,S* enantiomeric forms. *R,S*-*t*-butyl Josiphos is{(*R*)-1-[(*S*)-(diphenylphosphino)ferrocenyl]}ethyl-di-*tert*-butylphosphine of formula V below:



(V)

The ferrocenyl diphosphine ligands of formula III have two centers of asymmetry, and the process of the present invention is intended to encompass the use of single enantiomers, individual diastereomers, and mixtures of diastereomers thereof. The present invention is meant to comprehend the use of all such isomeric forms of the ligands of structural formula III for the asymmetric hydrogenation of a compound of formula II. The facial enantioselectivity of the hydrogenation reaction will depend on the particular stereoisomer of the ligand that is employed in the reaction. It is possible to control the configuration at the newly formed stereogenic center in a compound of formula I marked with an * by the judicious choice of the chirality of the ferrocenyl diphosphine ligand of formula III.

In one embodiment of the process of the present invention, R^1 is benzyl wherein the phenyl group of benzyl is unsubstituted or substituted one to three substituents selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy. In another embodiment of the process of the present invention, Z is NR^2R^3. In a class of this embodiment, NR^2R^3 is a heterocycle of the structural formula VI:



(VI)

wherein R^8 is hydrogen or C_{1-4} alkyl which is unsubstituted or substituted with one to five fluorines.

The asymmetric hydrogenation reaction of the present invention is carried out in a suitable organic solvent. Suitable organic solvents include lower alkanols, such as methanol, ethanol, isopropyl alcohol, and trifluoroethanol; tetrahydrofuran; methyl *t*-butyl ether; and aqueous mixtures thereof.

The reaction temperature for the reaction may be in the range of about 20 °C to about 90 °C. A preferred temperature range for the reaction is about 45 °C to about 65 °C.

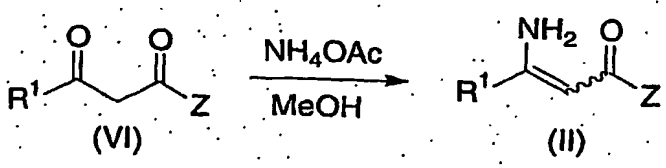
The hydrogenation reaction can be performed at a hydrogen pressure range of about 20 psi to about 1000 psi. A preferred hydrogen pressure range is about 80 psi to about 200 psi.

The transition metal catalytic species may be $[M(cod)Cl]_2$, $[M(norbornadiene)Cl]_2$, $[M(cod)_2]X$, or $[M(norbornadiene)_2]X$ wherein X is methanesulfonate, trifluoromethanesulfonate, tetrafluoroborate, hexafluorophosphate, or hexafluoroantimonate and M is rhodium (Rh), iridium (Ir), or ruthenium (Ru). A preferred catalyst when M is Rh is $[Rh(cod)Cl]_2$.

The ratio of substrate to catalyst is about 0.01 to about 10 mol %. A preferred substrate to catalyst ratio is about 0.05 mol % to about 0.4 mol %.

The beta-amino acrylic acid derivative precursors contain an olefinic double bond, and unless specified otherwise, are meant to include both *E* and *Z* geometric isomers or mixtures thereof as starting materials. The squiggly bond in the substrate of structural formula II signifies either the *Z* or *E* geometric isomer or a mixture thereof.

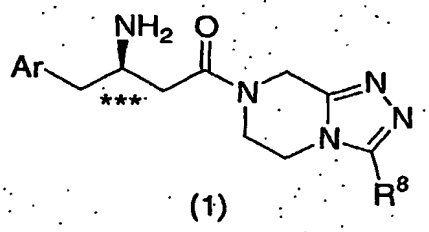
The beta-amino acid substrates of formula II for the asymmetric hydrogenation reaction of the present invention can be prepared from a beta-keto acid ester or amide of structural formula VI by reaction with a source of ammonia in a suitable organic solvent such as methanol, ethanol, isopropyl alcohol, tetrahydrofuran, and aqueous mixtures thereof.



(VI) (II)

Sources of ammonia include ammonium acetate, ammonium hydroxide, and ammonium formate. In one embodiment the source of ammonia is ammonium acetate.

Another embodiment of the present invention concerns a process for the preparation of a compound of structural formula I:



(1)

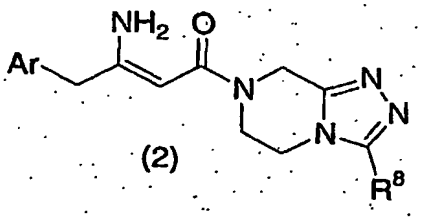
having the (*R*)-configuration at the stereogenic center marked with an ***;
in an enantiomeric excess of at least 70% over the enantiomer having the opposite (*S*)-configuration, wherein

Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy; and

R^8 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines;

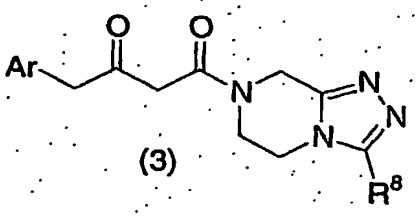
comprising the steps of:

(a) producing a compound of structural formula 2:



(2)

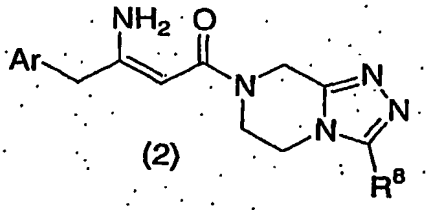
by treating a compound of structural formula 3:



(3)

with a source of ammonia in a suitable organic solvent; and

(b) hydrogenating a compound of structural formula 2:



(2)

in the presence of a rhodium catalyst and a (*R*,*S*)-Josiphos ligand in a suitable organic solvent.

In a class of this embodiment, Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl. In a subclass of this class, R8 is trifluoromethyl.

In another class of this embodiment, the rhodium catalyst is chloro(1,5-cyclooctadiene)rhodium(I) dimer {[Rh(cod)Cl]2}.

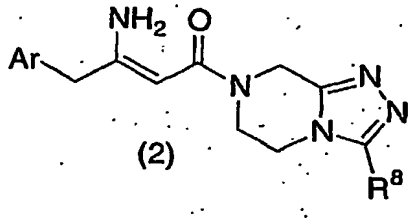
In another class of this embodiment, the (*R*,*S*)-Josiphos ligand is *R*,*S*-*t*-butyl Josiphos. In a subclass of this class, the rhodium catalyst is chloro(1,5-cyclooctadiene)rhodium(I) dimer.

In yet another class of this embodiment, Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl, R8 is trifluoromethyl, the rhodium catalyst is chloro(1,5-cyclooctadiene)rhodium(I) dimer, and the (*R*,*S*)-Josiphos ligand is *R*,*S*-*t*-butyl Josiphos.

In another embodiment the compound of structural formula 1 is obtained with an enantiomeric excess of greater than 90%. In a class of this embodiment the compound of structural formula 1 is obtained with an enantiomeric excess of greater than 95%.

Compounds of structural formula 1 are disclosed in WO 03/004498 (published 16 January 2003) as inhibitors of dipeptidyl peptidase-IV which are useful for the treatment of type 2 diabetes.

A further embodiment of the present invention comprises structurally novel intermediates of structural formula 2 which are useful in the preparation of compounds of structural formula 1:



(2)

wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy; and

R8 is hydrogen or C1-4 alkyl unsubstituted or substituted with one to five fluorines.

In a class of this embodiment of novel intermediates of formula 2, Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl and R^8 is trifluoromethyl.

Throughout the instant application, the following terms have the indicated meanings:

The term "% enantiomeric excess" (abbreviated "ee") shall mean the % major enantiomer less the % minor enantiomer. Thus, a 70% enantiomeric excess corresponds to formation of 85% of one enantiomer and 15% of the other. The term "enantiomeric excess" is synonymous with the term "optical purity."

The process of the present invention provides compounds of structural formula I with high optical purity, typically in excess of 70% ee. In one embodiment, compounds of formula I are obtained with an optical purity in excess of 80% ee. In a class of this embodiment, compounds of formula I are obtained with an optical purity in excess of 90% ee. In a subclass of this class, compounds of formula I are obtained with an optical purity in excess of 95% ee.

The term "enantioselective" shall mean a reaction in which one enantiomer is produced (or destroyed) more rapidly than the other, resulting in the predominance of the favored enantiomer in the mixture of products.

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like. The alkyl groups are unsubstituted or substituted with one to three groups independently selected from the group consisting of halogen, hydroxy, carboxy, aminocarbonyl, amino, C_{1-4} alkoxy, and C_{1-4} alkylthio.

The term "cycloalkyl" is intended to mean cyclic rings of alkanes of five to twelve total carbon atoms, or any number within this range (i.e., cyclopentyl, cyclohexyl, cycloheptyl, etc).

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine, and iodine.

The abbreviation "cod" means "1,5-cyclooctadiene."

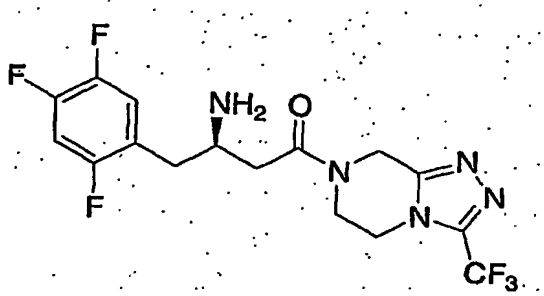
The term "aryl" includes phenyl and naphthyl. "Aryl" is unsubstituted or substituted with one to five substituents independently selected from fluoro, hydroxy, trifluoromethyl, amino, C_{1-4} alkyl, and C_{1-4} alkoxy.

The term "heteroaryl" means a 5- or 6-membered aromatic heterocycle that contains at least one ring heteroatom selected from O, S and N. Heteroaryls also

include heteroaryls fused to other kinds of rings, such as aryls, cycloalkyls and heterocycles that are not aromatic. Examples of heteroaryl groups include, but are not limited to, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridinyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, triazinyl, thienyl, pyrimidinyl, pyrazinyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, dihydrobenzofuranyl, indolinyl, pyridazinyl, indazolyl, isoindolyl, dihydrobenzothienyl, indolizinyl, cinnolinyl, phthalazinyl, quinazolinyl, naphthyridinyl, carbazolyl, benzodioxolyl, quinoxalinyl, purinyl, furazanyl, isobenzylfuranyl, benzimidazolyl, benzofuranyl, benzothienyl, quinolyl, indolyl, isoquinolyl, and dibenzofuranyl. "Heteroaryl" is unsubstituted or substituted with one to five substituents independently selected from fluoro, hydroxy, trifluoromethyl, amino, C_{1-4} alkyl, and C_{1-4} alkoxy.

Representative experimental procedures utilizing the novel process are detailed below. For purposes of illustration, the following Example is directed to the preparation of 2-5, but doing so is not intended to limit the process of the present invention to the specific conditions for making this particular compound.

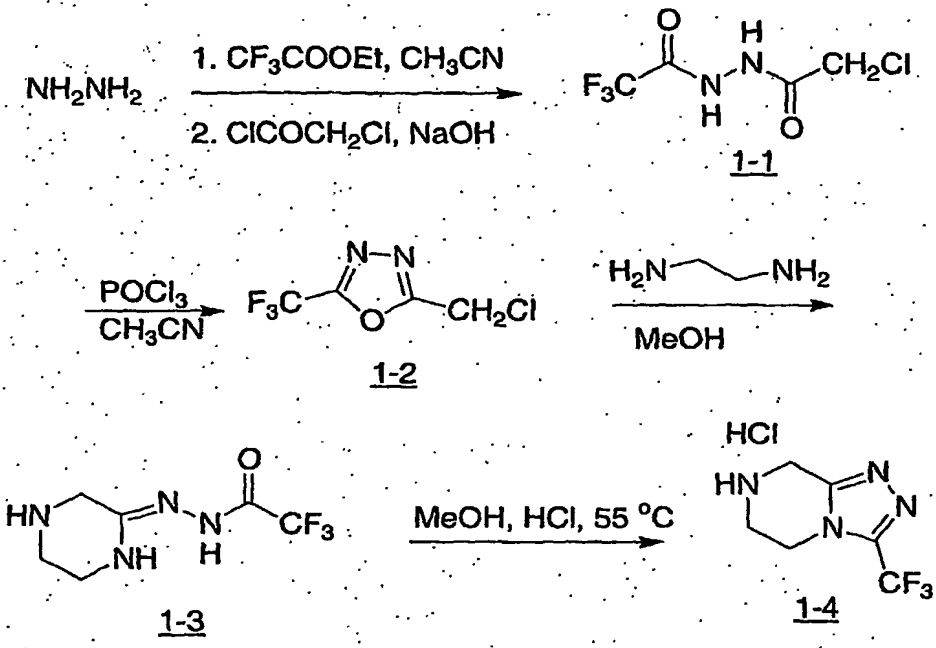
EXAMPLE



(2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine (2-5)

Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (1-4)

Scheme 1



Step A: Preparation of bishydrazide (1-1)

Hydrazine (20.1 g, 35 wt% in water, 0.22 mol) was mixed with 310 mL of acetonitrile. 31.5 g of ethyl trifluoroacetate (0.22 mol) was added over 60 min. The internal temperature was increased to 25 °C from 14 °C. The resulting solution was aged at 22 - 25 °C for 60 min. The solution was cooled to 7 °C. 17.9 g of 50 wt% aqueous NaOH (0.22 mol) and 25.3 g of chloroacetyl chloride (0.22 mol) were added simultaneously over 130 min at a temperature below 16 °C. When the reaction was complete, the mixture was vacuum distilled to remove water and ethanol at 27 ~ 30 °C and under 26 ~ 27 in Hg vacuum. During the distillation, 720 mL of acetonitrile was added slowly to maintain constant volume (approximately 500 mL). The slurry was filtered to remove sodium chloride. The cake was rinsed with about 100 mL of acetonitrile. Removal of the solvent afforded bis-hydrazide 1-1 (43.2 g, 96.5% yield, 94.4 area% pure by HPLC assay).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.2 (s, 2H), 10.7 (s, 1H), and 11.6 (s, 1H) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6): δ 41.0, 116.1 (q, J = 362 Hz), 155.8 (q, J = 50 Hz), and 165.4 ppm.

Step B: Preparation of 5-(trifluoromethyl)-2-(chloromethyl)-1,3,4-oxadiazole

(1-2)

Bishydrazide 1-1 from Step A (43.2 g, 0.21 mol) in ACN (82 mL) was cooled to 5 °C. Phosphorus oxychloride (32.2 g, 0.21 mol) was added, maintaining the temperature below 10 °C. The mixture was heated to 80 °C and aged at this temperature for 24 h until HPLC showed less than 2 area% of 1-1. In a separate vessel, 260 mL of IPAc and 250 mL of water were mixed and cooled to 0 °C. The reaction slurry was charged to the quench keeping the internal temperature below 10 °C. After the addition, the mixture was agitated vigorously for 30 min, the temperature was increased to room temperature and the aqueous layer was cut. The organic layer was then washed with 215 mL of water, 215 mL of 5 wt% aqueous sodium bicarbonate and finally 215 mL of 20 wt% aqueous brine solution. HPLC assay yield after work up was 86-92%. Volatiles were removed by distillation at 75-80 mm Hg, 55 °C to afford an oil which could be used directly in Step C without further purification. Otherwise the product can be purified by distillation to afford 1-2 in 70-80% yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.8 (s, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 32.1, 115.8 (q, J = 337 Hz), 156.2 (q, J = 50 Hz), and 164.4 ppm.

Step C: Preparation of N-[(2Z)-piperazin-2-ylidene]trifluoroacetohydrazide (1-3)

To a solution of ethylenediamine (33.1 g, 0.55 mol) in methanol (150 mL) cooled at –20 °C was added distilled oxadiazole 1-2 from Step B (29.8 g, 0.16 mol) while keeping the internal temperature at –20 °C. After the addition was complete, the resulting slurry was aged at –20 °C for 1 h. Ethanol (225 mL) was then charged and the slurry slowly warmed to –5 °C. After 60 min at –5 °C, the slurry was filtered and washed with ethanol (60 mL) at –5 °C. Amidine 1-3 was obtained as a white solid in 72% yield (24.4 g, 99.5 area wt% pure by HPLC).

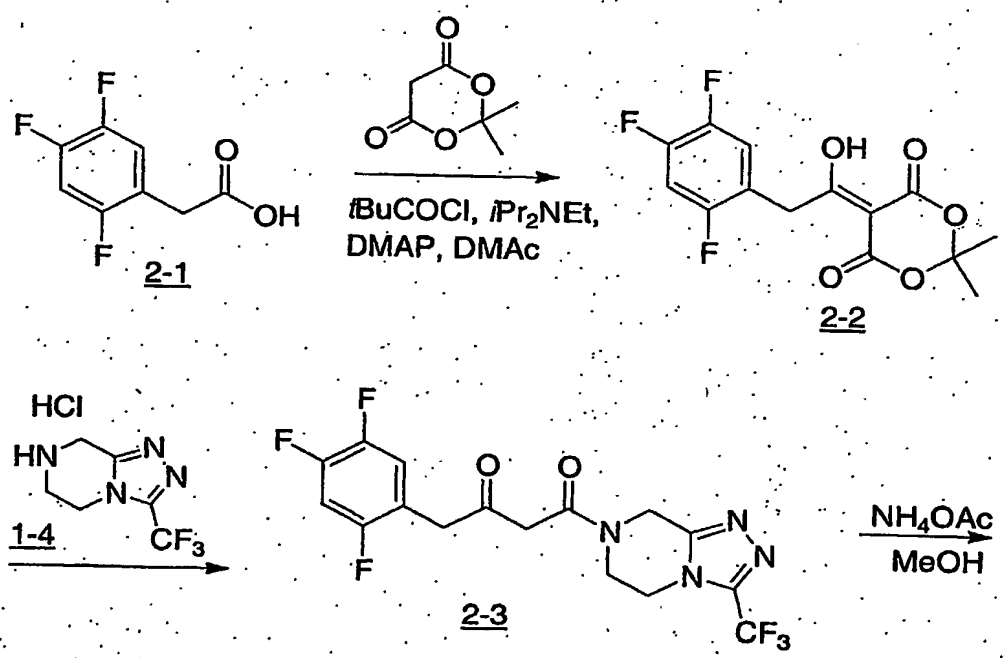
^{1}H-NMR (400 MHz, DMSO-*d*6): δ 2.9 (t, 2H), 3.2 (t, 2H), 3.6 (s, 2H), and 8.3 (b, 1H) ppm. ^{13}C-NMR (100 MHz, DMSO-*d*6): δ 40.8, 42.0, 43.3, 119.3 (q, J = 350 Hz), 154.2, and 156.2 (q, J = 38 Hz) ppm.

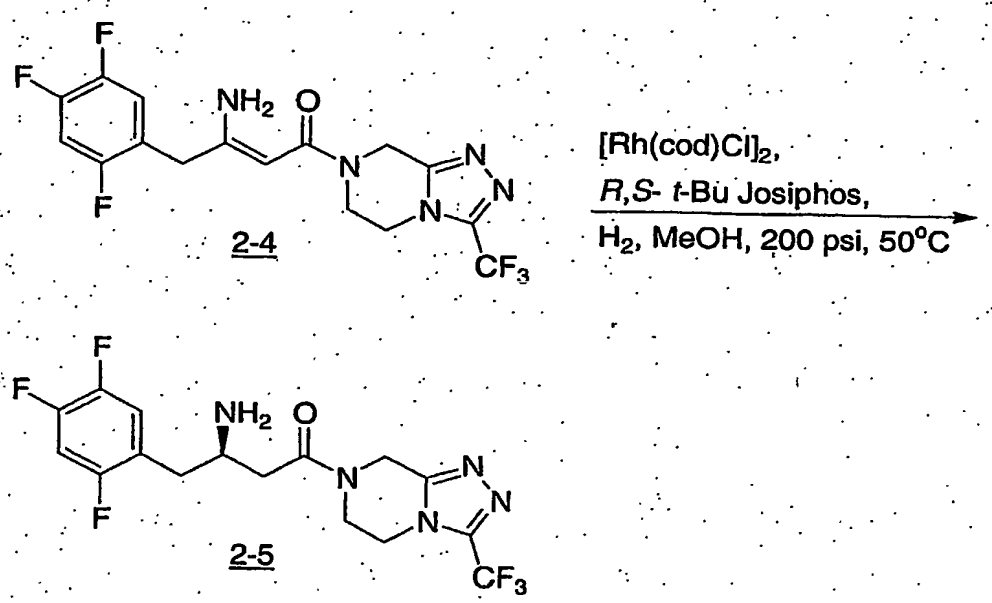
Step D: Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (1-4)

A suspension of amidine 1-3 (27.3 g, 0.13 mol) in 110 mL of methanol was warmed to 55 °C. 37% Hydrochloric acid (11.2 mL, 0.14 mol) was added over 15 min at this temperature. During the addition, all solids dissolved resulting in a clear solution. The reaction was aged for 30 min. The solution was cooled down to 20 °C and aged at this temperature until a seed bed formed (10 min to 1 h). 300 mL of MTBE was charged at 20 °C over 1 h. The resulting slurry was cooled to 2 °C, aged for 30 min and filtered. Solids were washed with 50 mL of ethanol:MTBE (1:3) and dried under vacuum at 45 °C. Yield of triazole 1-4 was 26.7 g (99.5 area wt% pure by HPLC).

^{1}H-NMR (400 MHz, DMSO-*d6*): δ 3.6 (t, 2H), 4.4 (t, 2H), 4.6 (s, 2H), and 10.6 (b, 2H) ppm; ^{13}C-NMR (100 MHz, DMSO-*d6*): δ: 39.4, 39.6, 41.0, 118.6 (q, J = 325 Hz), 142.9 (q, J = 50 Hz), and 148.8 ppm.

Scheme 2





Step A: Preparation of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-one (2-3)

2,4,5-Trifluorophenylacetic acid (2-1) (150 g, 0.789 mol), Meldrum's acid (125 g, 0.868 mol), and 4-(dimethylamino)pyridine (DMAP) (7.7 g, 0063 mol) were charged into a 5 L three-neck flask. *N,N*-Dimethylacetamide (DMAc) (525 mL) was added in one portion at room temperature to dissolve the solids. *N,N*-diisopropylethylamine (282 mL, 1.62 mol) was added in one portion at room temperature while maintaining the temperature below 40 °C. Pivaloyl chloride (107 mL, 0.868 mol) was added dropwise over 1 to 2 h while maintaining the temperature between 0 and 5 °C. The reaction mixture was aged at 5 °C for 1 h. Triazole hydrochloride 1-4 (180 g, 0.789 mol) was added in one portion at 40-50 °C. The reaction solution was aged at 70 °C for several h. 5% Aqueous sodium hydrogencarbonate solution (625 mL) was then added dropwise at 20 – 45 °C. The batch was seeded and aged at 20 – 30 °C for 1-2 h. Then an additional 525 mL of 5% aqueous sodium hydrogencarbonate solution was added dropwise over 2-3 h. After aging several h at room temperature, the slurry was cooled to 0 – 5 °C and aged 1 h before filtering the solid. The wet cake was displacement-washed with 20% aqueous DMAc (300 mL), followed by an additional two batches of 20% aqueous DMAc (400

mL), and finally water (400 mL). The cake was suction-dried at room temperature. The isolated yield of final product 2-3 was 89%.

Step B: Preparation of (2*Z*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)but-2-en-2-amine (2-4)

A 5 L round-bottom flask was charged with methanol (100 mL), the ketoamide 2-3 (200 g), and ammonium acetate (110.4 g). Methanol (180 mL) and 28% aqueous ammonium hydroxide (58.6 mL) were then added keeping the temperature below 30 °C during the addition. Additional methanol (100 mL) was added to the reaction mixture. The mixture was heated at reflux temperature and aged for 2 h. The reaction was cooled to room temperature and then to about 5 °C in an ice-bath. After 30 min, the solid was filtered and dried to afford 2-4 as a solid (180 g); m.p. 271.2 °C.

Step C: Preparation of (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine (2-5)

Into a 500 ml flask were charged chloro(1,5-cyclooctadiene)rhodium(I) dimer {[Rh(cod)Cl]2}(292 mg, 1.18 mmol) and (*R,S*) *t*-butyl Josiphos (708 mg, 1.3 mmol) under a nitrogen atmosphere. Degassed MeOH was then added (200 mL) and the mixture was stirred at room temperature for 1 h. Into a 4 L hydrogenator was charged the enamine amide 2-4 (118 g, 0.29 mol) along with MeOH (1 L). The slurry was degassed. The catalyst solution was then transferred to the hydrogenator under nitrogen. After degassing three times, the enamine amide was hydrogenated under 200 psi hydrogen gas at 50 °C for 13 h. Assay yield was determined by HPLC to be 93% and optical purity to be 94% ee.

The optical purity was further enhanced in the following manner. The methanol solution from the hydrogenation reaction (18 g in 180 mL MeOH) was concentrated and switched to methyl *t*-butyl ether (MTBE) (45 mL). Into this solution was added aqueous H_3PO_4 solution (0.5 M, 95 mL). After separation of the layers, 3*N* NaOH (35 mL) was added to the water layer, which was then extracted with MTBE (180 mL + 100 mL). The MTBE solution was concentrated and solvent switched to hot toluene (180 mL, about 75 °C). The hot toluene solution was then

allowed to cool to 0 °C slowly (5 – 10 h). The crystals were isolated by filtration (13 g, yield 72%, 98 – 99% ee); m.p. 114.1 – 115.7 °C.

^{1}H NMR (300 MHz, CD_3CN): δ 7.26 (m), 7.08 (m), 4.90 (s), 4.89 (s), 4.14 (m), 3.95 (m), 3.40 (m), 2.68 (m), 2.49 (m), 1.40 (bs).

Compound 2-5 exists as amide bond rotamers. Unless indicated, the major and minor rotamers are grouped together since the carbon-13 signals are not well resolved:

^{13}C NMR (CD_3CN): δ 171.8, 157.4 (ddd , J_{CF} = 242.4, 9.2, 2.5 Hz), 152.2 (major), 151.8 (minor), 149.3 (ddd; J_{CF} = 246.7, 14.2, 12.9 Hz), 147.4 (ddd, J_{CF} = 241.2, 12.3, 3.7 Hz), 144.2 (q, J_{CF} = 38.8 Hz), 124.6 (ddd , J_{CF} = 18.5, 5.9, 4.0 Hz), 120.4 (dd , J_{CF} = 19.1, 6.2 Hz), 119.8 (q, J_{CF} = 268.9 Hz), 106.2 (dd , J_{CF} = 29.5, 20.9 Hz), 50.1, 44.8, 44.3 (minor), 43.2 (minor), 42.4, 41.6 (minor), 41.4, 39.6, 38.5 (minor), 36.9.

The following high-performance liquid chromatographic (HPLC) conditions were used to determine percent conversion to product:

Column: Waters Symmetry C18, 250 mm x 4.6 mm

Eluent: Solvent A: 0.1 vol% $HClO_4/H_2O$

Solvent B: acetonitrile

Gradient: 0 min 75% A : 25% B

10 min 25% A : 75% B

12.5 min 25% A : 75% B

15 min 75% A : 25% B

Flow rate: 1 mL/min

Injection Vol.: 10 µL

UV detection: 210 nm

Column temp.: 40 °C

Retention times: compound 1-4: 9.1 min

compound 1-5: 5.4 min

*t*Bu Josiphos: 8.7 min

The following high-performance liquid chromatographic (HPLC) conditions were used to determine optical purity:

Column: Chirapak, AD-H, 250 mm x 4.6 mm

Eluent: Solvent A: 0.2 vol.% diethylamine in heptane

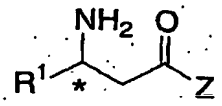
Solvent B: 0.1 vol% diethylamine in ethanol

Isochratic Run Time: 18 min

Flow rate: 0.7 mL/min
Injection Vol.: 7 µL
UV detection: 268 nm
Column temp.: 35 °C
Retention times: (*R*)-amine 1-5: 13.8 min
(*S*)-amine 1-5: 11.2 min

WHAT IS CLAIMED IS:

1. A process for preparing a compound of structural formula I:



(I)

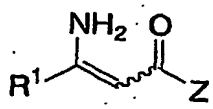
having the (*R*)- or (*S*)- configuration at the stereogenic center marked with an *; in an enantiomeric excess of at least 70% over the opposite enantiomer, wherein Z is OR^2, SR^2, or NR^2R^3;

R^1 is C_{1-8} alkyl, aryl, heteroaryl, aryl-C_{1-2} alkyl, or heteroaryl-C_{1-2} alkyl;

R^2 and R^3 are each independently hydrogen, C_{1-8} alkyl, aryl, or aryl-C_{1-2} alkyl; or

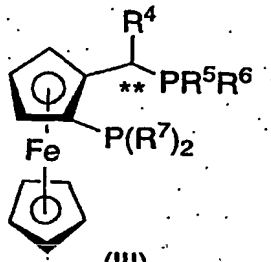
R^2 and R^3 together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclic ring system optionally containing an additional heteroatom selected from O, S, and NC_{1-4} alkyl, said heterocyclic ring system being optionally fused with a 5- to 6-membered saturated or aromatic carbocyclic ring system or a 5- to 6-membered saturated or aromatic heterocyclic ring system containing one to two heteroatoms selected from O, S, and NC_{1-4} alkyl, said fused ring system being unsubstituted or substituted with one to two substituents selected from hydroxy, amino, fluorine, C_{1-4} alkyl, C_{1-4} alkoxy, and trifluoromethyl;

comprising the step of hydrogenating a prochiral enamine of structural formula II:



(II)

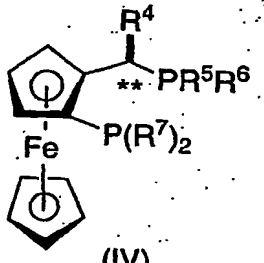
in a suitable organic solvent in the presence of a transition metal catalyst complexed to a chiral ferrocenyl diphosphine ligand of structural formula III:



(III)

wherein R^4 is C_{1-4} alkyl or aryl;
R^5 and R^6 are each independently C_{1-6} alkyl, C_{5-12} cycloalkyl, or aryl; and
R^7 is C_{1-4} alkyl or aryl.

2. The process of Claim 1 wherein said ferrocenyl diphosphine ligand is of structural formula IV:



(IV)

wherein the stereogenic center marked with an ** has the (*R*)-configuration.

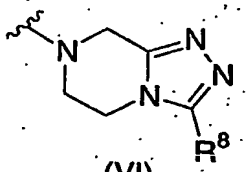
3. The process of Claim 2 wherein R^4 is C_{1-2} alkyl, R^5 and R^6 are C_{1-4} alkyl, and R^7 is phenyl.

4. The process of Claim 3 wherein R^4 is methyl, R^5 and R^6 are *t*-butyl, and R^7 is phenyl.

5. The process of Claim 1 wherein R^1 is benzyl wherein the phenyl group of benzyl is unsubstituted or substituted one to three substituents selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy.

6. The process of Claim 1 wherein Z is NR^2R^3.

7. The process of Claim 6 wherein NR^2R^3 is a heterocycle of the structural formula VI:



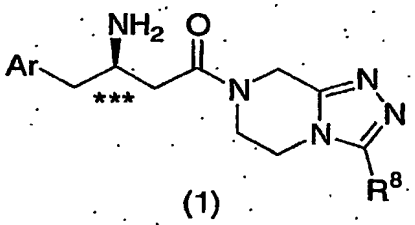
(VI)

wherein R^8 is hydrogen or C_{1-4} alkyl which is unsubstituted or substituted with one to five fluorines.

8. The process of Claim 1 wherein said transition metal catalyst is $[M(cod)Cl]_2$, $[M(norbornadiene)Cl]_2$, $[M(cod)_2]X$, or $[M(norbornadiene)_2]X$ wherein X is methanesulfonate, trifluoromethanesulfonate, tetrafluoroborate, hexafluorophosphate, or hexafluoroantimonate and M is rhodium, iridium, or ruthenium.

9. The process of Claim 8 wherein said transition metal catalyst is $[Rh(cod)Cl]_2$.

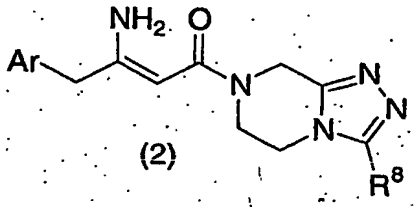
10. A process for preparing a compound of structural formula 1:



(1)

having the (*R*)-configuration at the stereogenic center marked with an ***;
in an enantiomeric excess of at least 70% over the enantiomer having the opposite (*S*)-configuration; wherein
Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy; and
R^8 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines;

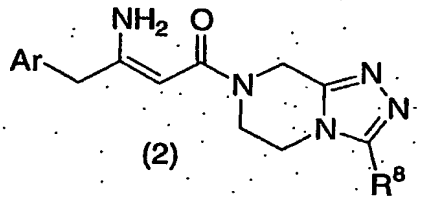
comprising the step of:
hydrogenating a compound of structural formula 2:



(2)

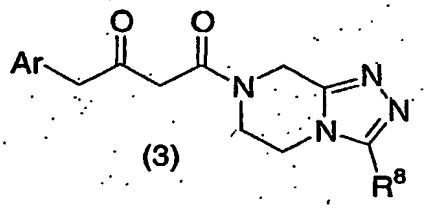
in the presence of a rhodium catalyst and a (*R*,*S*)-Josiphos ligand in a suitable organic solvent.

11. The process of Claim 10 additionally comprising the step of producing a compound of structural formula 2:



(2)

by treating a compound of structural formula 3:



(3)

with a source of ammonia in a suitable organic solvent.

12. The process of Claim 10 wherein Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl and R^8 is trifluoromethyl.

13. The process of Claim 10 wherein said rhodium catalyst is $[Rh(cod)Cl]_2$.

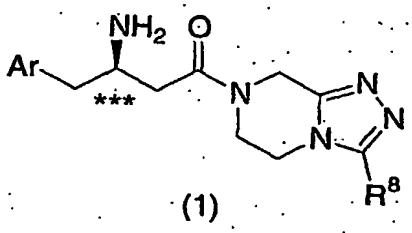
14. The process of Claim 10 wherein said (*R*,*S*)-Josiphos ligand is *R*,*S*-*t*-butyl Josiphos.

15. The process of Claim 14 wherein said rhodium catalyst is $[Rh(cod)Cl]_2$.

16. The process of Claim 10 wherein Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl, R^8 is trifluoromethyl, said rhodium catalyst is $[Rh(cod)Cl]_2$, and said (*R*,*S*)-Josiphos ligand is *R*,*S*-*t*-butyl Josiphos.

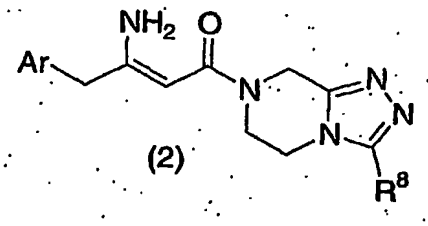
17. The process of Claim 11 wherein said source of ammonia is ammonium acetate.

18. A process for preparing a compound of structural formula 1:



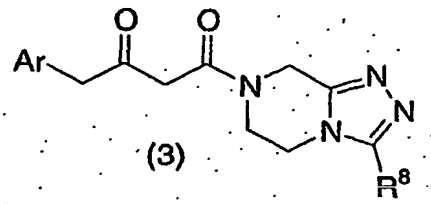
(1)

having the (*R*)-configuration at the stereogenic center marked with an ***;
in an enantiomeric excess of at least 70% over the enantiomer having the opposite (*S*)-configuration; wherein
Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy; and
R^8 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines;
comprising the steps of:
(a) producing a compound of structural formula 2:



(2)

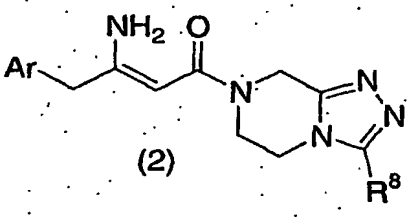
by treating a compound of structural formula 3:



(3)

with a source of ammonia in a suitable organic solvent; and

(b) hydrogenating a compound of structural formula 2:



(2)

in the presence of a rhodium catalyst and a (*R*,*S*)-Josiphos ligand in a suitable organic solvent.

TITLE OF THE INVENTION

PROCESS TO CHIRAL BETA-AMINO ACID DERIVATIVES BY ASYMMETRIC HYDROGENATION

ABSTRACT OF THE DISCLOSURE

The present invention relates to a process for the efficient preparation of enantiomerically enriched beta-amino acid derivatives which are useful in the asymmetric synthesis of biologically active molecules. The process comprises an enantioselective hydrogenation of a prochiral beta-amino acrylic acid derivative precursor in the presence of a rhodium catalyst complexed with a chiral ferrocenyl diphosphine ligand.

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLORED OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REPERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning documents *will not* correct images problems checked, please do not report the problems to the IFW Image Problem Mailbox